NEW MODELS OF AB OLIGOMER-INDUCED COGNITIVE IMPAIRMENT AND SYNAPTIC DEGENERATION FOR MOLECULE SCREENING AND THERAPEUTIC TARGETS IDENTIFICATION

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Introduction: The development of efficient therapeutics for Alzheimer’s disease (AD) represents one of the biggest unmet medical needs today. SynAging is a spin-off in neurosciences providing pertinent innovative models and time-efficient technologies for the development of protective strategies targeting AD, most particularly at early stages. Contrary to classical models focusing on amyloid plaques (transgenic mice or animals exposed to fibrillar Aβ), we used soluble Aβ oligomers to develop in vitro and in vivo models proposed to identify specific therapeutic targets and to validate neuroprotective molecules.

Aim: To assess the interest of our models in identifying two novel protective GPCRx ligands (SynA11x and SynA21x) from our pipeline of original molecules.

Methods: The neuroprotective potential of SynA11x and SynA21x was investigated in mice primary neurons exposed to Aβ oligomers. Neurodegeneration was monitored by MTT assay, DAPI and tubulin staining, as well as measurement of caspase proteolytic activities and synaptic protein levels. Cognitive performances of soluble Aβ-injected mice were monitored by following immediate spatial working memory performance and learning and long-term memory capabilities.

Results: Primary neurons were protected from oligomeric Aβ-induced synaptic impairment and subsequent cell death by SynA11x and SynA21x, both being able to improve all cellular and biochemical parameters. Intracerebral administration of these molecules also led Aβ oligomer-infused mice to fully recover their cognitive performances, which was completely abolished upon GPRCx antisense oligonucleotide treatment.

Conclusion: In allowing discovering new GPCRx ligands, our models appeared powerful preclinical tools in the development of efficient AD-modifying strategies and in identification of potential therapeutic targets.